#4

Practitioner's Docket No. U 013589-7 *PATENT*

Optional Customer No. Bar Code

00140

PATENT TRADEMARK OFFICE

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

[ ] original.
[ ] design.

NOTE: With the exception of a supplemental oath or declaration submitted in a reissue, a supplemental oath or declaration is not treated as an amendment under 37 CFR 1.312 (Amendments after allowance). M.P.E.P. Section 714.16, 7th Ed.

[ ] supplemental.

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items.

[X] national stage of PCT.

NOTE: If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P.

NOTE: See 37 C.F.R. Section 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.

[ ] divisional.
[ ] continuation.

NOTE: Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C.F.R. Section 1.53(b) (application filing requirements-nonprovisional application).

[ ] continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: *If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.*

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) [ ] is attached hereto.

NOTE: *"The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:*

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60).

(b) [ ] was filed on _____, [ ] as Application No. _____
[ ] and was amended on _____ (if applicable).

NOTE: *Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 C.F.R. Section 1.67.*

NOTE: *"The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:*

(A) application number (consisting of the series code and the serial number, e.g., 08/123,456);
(B) serial number and filing date;
(C) attorney docket number which was on the specification as filed;
(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or
(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.
M.P.E.P. Section 601.01(a), 7th ed.

(c) [X] was described and claimed in PCT International Application No. PCT/GB00/00511 filed on 15 February 2000 and as amended under PCT Article 19 on _____*(if any)*.

SUPPLEMENTAL DECLARATION (37 C.F.R. Section 1.67(b))

(complete the following where a supplemental declaration is being submitted)

[ ] I hereby declare that the subject matter of the

[ ] attached amendment
[ ] amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, Section 1.56,

(also check the following items, if desired)

[ ] and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

[ ] in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 C.F.R. Section 1.98.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declaration as required by Section 1.63. The claim for priority and the certified copy of the foreign application specified in 35 U.S.C. Section 119(b) must be filed in the case of an interference (Section 1.630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted. If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in Section 1.17(i). If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner; or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 C.F.R. Section 1.55(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [X] such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U.S. itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, **MONTH**, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
GB	9903404.3	16 February 1999	[X]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. Section 119(e))

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER **FILING DATE**

_____/_____ _____
_____/_____ _____
_____/_____ _____

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. SECTION 120

[ ] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY,* FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

_____

NOTE: If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. Section 120.

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179

JOHN RICHARDS, 31053

RICHARD J. STREIT, 25765

PETER D. GALLOWAY, 27885

IAIN C. BAILLIE, 24090

RICHARD P. BERG, 28145

JULIAN H. COHEN, 20302

WILLIAM R. EVANS 25858

JANET I. CORD, 33778

CLIFFORD J. MASS, 30086

CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

[ ] I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

[ ] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

NOTE: "Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4)." Section 601.03, M.P.E.P., 7th Ed

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

NOTE: Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R. Section 1.63(a)(3).

NOTE: Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors. Section 1.63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor. 62 Fed. Reg. 53,131, 53,142, October 10, 1997.

1-00

Full name of sole or first inventor

Peter (*Given Name*) David (*Middle Initial or Name*) DAVIS (*Family (Or Last Name)*)

Inventor's signature (X) _____

Date (X) November 16th 2001 **Country of Citizenship** Great Britain

Residence 10 Aston Park, Aston Rowant, Watlington, OX9 5SW, G.B. GBR

Post Office Address Same as above

Full name of second joint inventor, if any

(*Given Name*) (*Middle Initial or Name*) (*Family (Or Last Name)*)

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

Full name of third joint inventor, if any

(*Given Name*) (*Middle Initial or Name*) (*Family (Or Last Name)*)

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[ ] **Signature** for fourth and subsequent joint inventors. *Number of pages added* ________

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* ________

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. Section 1.47. *Number of pages added* ________

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. Section 1.47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added ________________

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[X] This declaration ends with this page.

SEND CORRESPONDENCE TO

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)
William R. Evans
(212) 708-1930

(complete the following if applicable)

Since this filing is a [ ] continuation [ ] divisional there is attached hereto a Change of Correspondence Address so that there will be no question as to where the PTO should direct all correspondence.

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

09/890989

JC03 Rec'd PCT/PTC 0 8 AUG 2001

Practitioner's Docket No. U 013589-7

Optional Customer No. Bar Code

00140

PATENT TRADEMARK OFFICE

CHAPTER II

TRANSMITTAL LETTER
TO THE UNITED STATES ELECTED OFFICE (EO/US)
(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/00511	15 FEBRUARY 2000	16 FEBRUARY 1999

TITLE OF INVENTION

COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

APPLICANT(S)

PETER DAVID DAVIS

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: The completion of those filing requirements that can be made at a time later than 30 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 USC 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. §1.491 which states: "An international application enters the national state when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1.494 and § 1.495."

CERTIFICATION UNDER 37 C.F.R. 1.10*
(Express Mail label number is ***mandatory****.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date August 8, 2001, in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EL 728214420 US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

MARIA MELIAN
(type or print name of person mailing paper)

Maria Melian
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

****WARNING:*** *Each paper or fee filed by "Express Mail"* ***must*** *have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will ***not*** *be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

EXPRESS MAIL LABEL
NO.: EL 728214420 US

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. §1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULA-TIONS
[ ]*	TOTAL CLAIMS	15 - 20 =		x $ 18.00 =	$
	INDEPENDENT CLAIMS	5 - 3 =	2	x $ 80.00 =	160.00
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $270.00				
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) .... $100.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) .... $690.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) .... $710.00 [ ] has not been paid (37 CFR 1.492(a)(3)) .... $1,000.00 [X] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $860.00				
	Total of above Calculations				= 1,020.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Statement may also be filed. (note 37 CFR 1.9, 1.27, 1.28)				-
	Subtotal				
	Total National Fee				$1, 020.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL	Total Fees enclosed				$1,020.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. [X] A check in the amount of 1,020.00 to cover the above fees is enclosed.
ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

***WARNING:* *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
i. [X] by the International Bureau.
Date of mailing of the application (from form PCT/IB/308): _____.
ii. [ ] by applicant on _____.
Date

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [ ] is transmitted herewith.
b. [X] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____.
Date
d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. [ ] are transmitted herewith.
b. [X] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): ________.
   ii. [X] by applicant on 09/02/2000
   Date
c. [ ] have not been transmitted as
   i. [ ] applicant chose not to make amendments under PCT Article 19.
   Date of mailing of Search Report (from form PCT/ISA/210): MAY 25, 2000.
   ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PCT/IPEA/409)
[X] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
a. [X] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [X] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [X] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
    a. [ ] was previously submitted by applicant on ___________.
    Date
    b. [ ] is submitted herewith, and such oath or declaration
        i. [ ] is attached to the application.
        ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
    c. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
    a. [X] is transmitted herewith.
    b. [ ] has been transmitted by the International Bureau.
    Date of mailing (from form PCT/IB/308): _______________.
    c. [ ] is not required, as the application was searched by the United States International Searching Authority.
    d. [ ] will be transmitted promptly upon request.
    e. [ ] has been submitted by applicant on _______________.
    Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
    a. [ ] is transmitted herewith.
    Also transmitted herewith is/are:
    [ ] Form PTO-1449 (PTO/SB/08A and 08B).
    [ ] Copies of citations listed.
    b. [X] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
    c. [ ] was previously submitted by applicant on _______________.
    Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

14. [X] Additional documents:
    a. [ ] Copy of request (PCT/RO/101)
    b. [X] International Publication No. WO 00/48591
        i. [X] Specification, claims and drawing
        ii. [ ] Front page only
    c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
    d. [X] Other

FORM PCT/IPEA/408 (WRITTEN OPINION);
COPY OF REPLY TO THE WRITTEN OPINION DATED 10TH NOV. 2000

15. [X] The above checked items are being transmitted
    a. [X] before 30 months from any claimed priority date.
    b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on
_____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: *"A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).*

NOTE: *"Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).*

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425.

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[ ] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: *Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must*

only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[X] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).*

NOTE: *37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 25,858

WILLIAM R. EVANS
(type or print name of practitioner)

Tel. No.: (212)708-1930

LADAS & PARRY
P.O. Address

Customer No.: 00140

26 WEST 61ST STREET
NEW YORK, N.Y. 10023

Practitioner's Docket No. U 013589-7

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[X] In re application of: PETER DAVID **DAVIS**
Application No.: 09/890,989 Group No.:
Filed: AUGUST 8, 2001 Examiner:
For: COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

[ ] *Patent No.: Issue Date:

**NOTE: Insert name(s) of inventor(s) and title also for patent Where statement is with respect to a maintenance fee payment, also insert application number and filing date, and add Box M. Fee to address.*

STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(c-f) and 1.27(b-d))

With respect to the invention described in
[ ] the specification filed herewith.
[X] application no. 09/890,989, filed AUGUST 8, 2001.
[ ] patent no. _____ issued _____.

I. IDENTIFICATION AND RIGHTS AS A SMALL ENTITY

I hereby state that I am

(complete either (a), (b), (c) or (d) below)

(a) Independent Inventor
[ ] a below named independent inventor, and that I qualify as an independent inventor, as defined in 37 CFR 1.9(c), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office.

(b) Noninventor Supporting a Claim by Another
[ ] making this statement to support a claim by

_____

for a small entity status for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code. I hereby state that I would qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, if I had made the above identified invention.

(c) Small Business Concern
[ ] the owner of the small business concern identified below:
check one → [ ] an official of the small business concern empowered to act on behalf of the concern identified below:

Name of Concern ANGIOGENE PHARMACEUTICALS LTD.
Address of Concern 14 PLOWDEN PARK ASTON ROWANT
WATLINGTON, OXFORDSHIRE OX9 5SW, G.B. and
that the above identified small business concern qualifies as a small business concern, as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

(d) Non-Profit Organization
[ ] an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization _____
Address of Organization _____
_____
TYPE OF ORGANIZATION
[ ] University or Other Institution of Higher Education
[ ] Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3))

[ ] Nonprofit Scientific or Educational Under Statute of State of the United States of America
(Name of State_____)
(Citation of Statute_____)

[ ] Would Qualify as Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3)), if Located in the United States of America

[ ] Would Qualify as Nonprofit Scientific or Educational Under Statute of State of the United States of America, if Located in the United States of America
(Name of State_____)
(Citation of Statute_____)

and that the nonprofit organization identified above qualifies as a nonprofit organization, as defined in 37 CFR 1.9(e), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code.

II. OWNERSHIP OF INVENTION BY DECLARANT

I hereby state that rights under contract or law remain with and/or have been conveyed to the above identified

[ ] person	[X] concern	[ ] organization
(item (a) or (b) above)	(item (c) above)	(item (d) above)

EXCEPT, that if the rights held are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held (1) by any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, (2) any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or (3) a nonprofit organization under 37 CFR 1.9(e).

[X] no such person, concern, or organization
[ ] person, concerns or organizations listed below*

**NOTE:* *Separate statements are required from each named person, concern or organization having rights to the invention as to their status as small entities. (37 CFR 1.27)*

Full Name _____
Address _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

Full Name _____
Address _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

III. ACKNOWLEDGEMENT OF DUTY TO NOTIFY PTO OF STATUS CHANGE

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

IV. DECLARATION

(check the following item, if desired)

NOTE: *The following verification statement need not be made in accordance with the rules published on October 10, 1997, 62 Fed. Reg. 52131, effective December 1, 1997.*

NOTE: *"The presentation to the Office (whether by signing, filing, submitting, or later advocating) of any paper by a party, whether a practitioner or non-practitioner, constitutes a certification under § 10.18(b) of this chapter. Violations of § 10.18(b)(2) of this chapter by a party, whether a practitioner or non-practitioner, may result in the imposition of sanctions under § 10.18(c) of this chapter. Any practitioner violating § 10.18(b) may also be subject to disciplinary action. See §§ 10.18(d) and 10.23(c)(15)." 37 CFR 1.4(d)(2).*

[ ] I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

V. SIGNATURES

(complete only (e) or (f) below)

(e)
NOTE: All inventors must sign the statement.

_____
Name of Inventor

_____ Date: _____
Signature of Inventor

_____
Name of Inventor

_____ Date: _____
Signature of Inventor

_____
Name of Inventor

_____ Date: _____
Signature of Inventor

(add lines for any additional inventors who must sign)

or

(f)
NOTE: The title of the person signing on behalf of a concern or nonprofit organization should be specified.

Name of Person Signing (X) PETER DAVID DAVIS

Title of Person (X) DIRECTOR
(if signing on behalf of a concern or non-profit organization)

Address of Person Signing ANGIOGENE PHARMACEUTICALS LTD.

14 PLOWDEN PARK, ASTON ROWANT, WATLINGTON, OXFORDSHIRE OX9 5SW, G.B.

SIGNATURE (X) _____ DATE (X) November 26th 2001

#3/A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Peter David DAVIS
Serial No.: 09/890,989 Group No.:
Filed: August 8, 2001 Examiner.:
For: COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

Attorney Docket No.: U 013589-7

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Please amend the above application as follows:

IN THE CLAIMS

4. (amended) A composition according to claim 2 wherein the nitric oxide synthase inhibitor is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas or aminoguanidine.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOHN RICHARDS
(Type or print name of person mailing paper)

Date: August 29, 2001

(Signature of person mailing paper)

9. (amended) A composition according to claim 1 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

10. (amended) A composition according to claim 1 wherein the composition is in the form of a kit, one part of the kit containing the vascular damaging agent and the second part of the kit the nitric oxide inhibitor.

Please add the following claims:

16. (new) A composition according to claim 3 wherein the nitric oxide synthase inhibitor is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas or aminoguanidine.

17. (new) A composition according to claim 2 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

18. (new) A composition according to claim 3 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

19. (new) A composition according to claim 4 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

20. (new) A composition according to claim 5 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

REMARKS

The above amendatory action is taken solely for the purpose of avoiding claim fees that would otherwise accrue due to the presence of multiple dependent claims.

Respectfully submitted,

JOHN RICHARDS
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.31,053 (212)708-1915

MARKED UP COPY

4. (amended) A composition according to [claims 2 and 3] claim 2 wherein the nitric oxide synthase inhibitor is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas or aminoguanidine.

9. (amended) A composition according to [any one of claims 1 to 8] claim 1 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

10. (amended) A composition according to [any one of claims 1 to 9] claim 1 wherein the composition is in the form of a kit, one part of the kit containing the vascular damaging agent and the second part of the kit the nitric oxide inhibitor.

Practitioner's Docket No: U 013589-7 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Peter David DAVIS

Serial No.: 09/890,989 Group No.:

Filed: August 8, 2001 Examiner:

For: COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

Assistant commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT TRANSMITTAL

1. Transmitted herewith is an amendment for this application.

STATUS

2. Applicant is
   - ☒ a small entity. A statement:
     - ☐ is attached.
     - ☒ was already filed.
   - ☐ other than a small entity.

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☒ deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

FACSIMILE

☐ transmitted by facsimile to the Patent and Trademark Office.

Signature

Date: August 29, 2001

JOHN RICHARDS
(*type or print name of person certifying*)

EXTENSION OF TERM

NOTE: "Extension of Time in Patent Cases (Supplement Amendments) — If a timely and complete response has been filed after a Non-Final Office Action, an extension of time is not required to permit filing and/or entry of an additional amendment after expiration of the shortened statutory period.

If a timely response has been filed after a Final Office Action, an extension of time is required to permit filing and/or entry of a Notice of Appeal or filing and/or entry of an additional amendment after expiration of the shortened statutory period unless the timely-filed response placed the application in condition for allowance. Of course, if a Notice of Appeal has been filed within the shortened statutory period, the period has ceased to run." Notice of December 10, 1985 (1061 O.G. 34-35).

NOTE: See 37 C.F.R. 1.645 for extensions of time in interference proceedings, and 37 C.F.R. 1.550(c) for extensions of time in reexamination proceedings.

3. The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136 apply.

(complete (a) or (b), as applicable)

(a) ☐ Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(4)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
☐	one month	$ 110.00	$ 55.00
☐	two months	$ 390.00	$ 195.00
☐	three months	$ 890.00	$ 445.00
☐	four months	$ 1,390.00	$ 695.00

Fee: $_____

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

☐ An extension for _____ months has already been secured. The fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $_____

OR

(b) ☒ Applicant believes that no extension of term is required. However, this is a conditional petition being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. 1.16(b)-(d)) has been calculated as shown below:

(Col.1)		(Col. 2)	(Col. 3)	SMALL ENTITY			OTHER THAN A SMALL ENTITY	
Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Addit. Fee	*OR*	Rate	Addit. Fee
Total *	Minus	**	=	x $ 9 =	$		x $18 =	$
Indep. *	Minus	***	=	x $40 =	$		x $80 =	$
[ ] First Presentation of Multiple Dependent Claim				+ $135 =	$		+ $270 =	$
				Total Addit. Fee	$___	*OR*	Total Addit. Fee	$___

* If the entry in Col. 1 is less than the entry in Col. 2, write "O" in Col. 3,
** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest No. Previously Paid For" (Total or Indep.) is the highest number found in the appropriate box in Col. 1 of a prior amendment or the number of claims originally filed.

WARNING: *"After final rejection or action (§ 1.113) amendments may be made canceling claims or complying with any requirement of form which has been made." 37 C.F.R. 1.116(a) (emphasis added).*

(complete (c) or (d), as applicable)

(c) ☒ No additional fee for claims is required.

OR

(d) ☐ Total additional fee for claims required $ _____.

FEE PAYMENT

5. ☐ Attached is a check in the sum of $ _____.

☐ Charge Account No. 12-0425 the sum of $ _____.
A duplicate of this transmittal is attached.

FEE DEFICIENCY

NOTE: If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to charge the deposit account for any fee deficiency should be checked See the Notice of April 7, 1986, (1065 O.G. 31-33).

6. ☒ If any additional extension and/or fee is required, charge Account No. 12-0425.

AND/OR

☒ If any additional fee for claims is required, charge Account No. 12-0425

SIGNATURE OF PRACTITIONER

Reg. No. 31,053

JOHN RICHARDS
(type or print name of practitioner)

Tel. No. 212-708-1915

P.O. Address

Customer No. 00140

c/o Ladas & Parry
26 West 61 Street
New York, N.Y. 10023

COMBINATIONS FOR THE TREATMENT OF DISEASES INVOLVING ANGIOGENESIS

This invention relates to a method for treating diseases involving active angiogenesis, to compositions useful for the treatment of diseases involving angiogenesis and to the use of the compositions in the preparation of a medicament for the treatment of diseases involving active angiogenesis. In one aspect of the invention the method involves the administration to a mammal of an inhibitor of nitric oxide in combination with a compound inducing vascular damage.

Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763, 1995). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.

Certain chemical compounds have been shown to have vascular damaging activity against the newly formed endothelium of solid tumours. These agents include, for example, combretastatin A4 phosphate (Dark et al., Cancer Research 57, 1829-1834, 1997), combretastain analogues (for example those described in J Med Chem 41, 3022-32,1998 by Ohsumi et al.), the flavone acetic acids, for example 5,6-dimethylxanthenone acetic acid (Zwi, Pathology, 26, 161-9, 1994), colchicine (Baguley et al. Eur J Cancer 27, 482-7, 1991). However some tumours are resistant to these agents.

One characteristic of tumours relatively resistant to vascular damaging agents is their ability to produce large amounts of nitric oxide. The role of nitric oxide in tumour

growth is unclear and there have been reports of both tumour-stimulating and tumour-inhibiting effects (Chinje and Stratford, Essays Biochem. 32, 61-72, 1997). It has been suggested that the antitumour effects of 5,6-dimethylxanthenone acetic acid are mediated in part by nitric oxide production (Thompsen et al. Cancer Chemother Pharmacol. 31,151-5, 1992).

WO-A 9509621 and Br. J Cancer (1998), 77(3), 426-433 disclose combinations of cytokine releasing anticancer agents (TNF-releasing agents). These relate to ameliorating the effects of pro-inflammatory cytokines. There is no suggestion of synergistic activity from a combination of a vascular damaging agent (many of which have no pro-inflammatory activity) and an NO inhibitor.

We have found that the efficacy of vascular damaging agents can be improved by combining the treatment with inhibitors of the formation or action of nitric oxide in a mammalian system.

In particular the efficacy of vascular damaging agents can be improved by combination with inhibitors of nitric oxide synthases, the enzymes that produce nitric oxide from arginine. In particular the efficacy of vascular damaging agents against tumours relatively resistant to their effects is improved by treatment with a nitric oxide synthase inhibitor.

Accordingly in one aspect of the invention we provide a method of treatment for a mammal having a disease that involves active angiogenesis such method comprising the administration of a therapeutic or subtherapeutic amount of a vascular damaging agent together with an inhibitor of nitric oxide synthase in an amount sufficient to augment the effect of the vascular damaging agent. The method is useful for the treatment of diseases such as cancers, especially solid tumours, psoriasis, diabetic retinopathy, macular degeneration, atherosclerosis and rheumatoid arthritis.

The vascular damaging agent and the nitric oxide synthase inhibitor can be administered together or separately. The method may be used as a sole therapy or in

combination with other treatments. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example

adriamycin and bleomycin; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab; and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

The vascular damaging agent and the nitric oxide synthase inhibitor can be administered by the same route or by different routes. Such routes of administration include oral, buccal, nasal, topical, rectal and parenteral administration. Each component of the method, the vascular damaging agent and the nitric oxide synthase inhibitor may independently be administered in a form suitable for the intended route of administration and such forms may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.
The preferred route of administration of each component will depend on the disease being treated. For solid tumours the components may each advantageously be delivered, either together or separately, as an intravenous infusion.

Vascular damaging agents are compounds which induce selective damage to newly formed, rather than established, vasculature. Many such compounds are known and it is considered this invention is generally applicable to such agents. Such agents include tubulin-binding agents, for example the combretastatins and their prodrugs, the colchinols and their prodrugs and (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenylamine and its prodrugs, TNF-alpha inducing agents such as the xanthenone acetic acids, for example dimethylxanthenoneacetic acid, and antibodies targeted to the vasculature.

A wide variety of compounds which inhibit the formation or action of nitric oxide in mammalian systems can be employed. Specifically nitric oxide synthase inhibitors are those compounds which inhibit any of the forms of nitric oxide synthase. Such agents include derivatives of arginine, ornithine, lysine and citrulline, S-alkylthioureas and aminoguanidines. Where the nitric oxide synthase inhibitor is a derivative of arginine it may be, for example, an N^G-substituted L-arginine selected from N^G-nitro-L-arginine and alkyl esters thereof, N^G-methyl-L-arginine and N^G-amino-L-arginine. Where the nitric oxide synthase inhibitor is a derivative of ornithine it may be, for example L-N6-(1-iminoethyl)-ornithine. Where the nitric oxide synthase inhibitor is a derivative of lysine it may be, for example L-N6-(1-iminoethyl)-lysine. Where the nitric oxide synthase inhibitor is a derivative of citrulline it may be, for example L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline such as S-methyl-L-thiocitrulline.

In a further embodiment of the invention there is provided a composition for the treatment of diseases involving active angiogenesis. The composition of the invention comprises a vascular damaging agent in combination with a nitric oxide synthase inhibitor where both the vascular damaging agent and the nitric oxide synthase inhibitor are as hereinbefore defined.

Thus for example the composition may contain for example a combretastatin derivative, a colchicine derivative, a colchinol derivative, a xanthenone acetic acid derivative or a vascular targeted antibody, in combination with a nitric oxide synthase inhibitor for example a derivative of arginine, a derivative of ornithine, a derivative of lysine, a derivative of citrulline, a S-alkylthioureas or an aminoguanidine.

Particular examples of vascular damaging agents that may be present in the composition include combretastatin A4 and its prodrugs for example combretastatin A4 phosphate, (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenylamine and its prodrugs, N-acetylcolchinol and its prodrugs for example N-acetylcolchinol-O-phosphate and 5,6-dimethylxanthenoneacetic acid.

Particular examples of nitric oxide synthase inhibitors which may be present in the composition include derivatives of arginine, ornithine, lysine and citrulline, S-alkylthioureas aminoguanidines and aminopyridines. Where the nitric oxide synthase inhibitor is a derivative of arginine it may be, for example, an N^G-substituted L-arginine selected from N^G-nitro-L-arginine and alkyl esters thereof, N^G-methyl-L-arginine and N^G-amino-L-arginine. Where the nitric oxide synthase inhibitor is a derivative of ornithine it may be, for example L-N6-(1-iminoethyl)-ornithine. Where the nitric oxide synthase inhibitor is a derivative of lysine it may be, for example L-N6-(1-iminoethyl)-lysine. Where the nitric oxide synthase inhibitor is a derivative of citrulline it may be, for example L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline such as S-methyl-L-thiocitrulline. Where the nitric oxide synthase inhibitor is an aminopyridine it may be for example 2-amino-4-methylpyridine.

The composition is useful for the treatment of diseases involving active angiogenesis for example solid tumours, psoriasis, diabetic retinopathy, macular degeneration, atherosclerosis and rheumatoid arthritis.

The relative proportion of each component will be determined by the identity of each individual vascular damaging agent or nitric oxide synthase inhibitor and by the disease to be treated.

The composition may include pharmaceutically acceptable excipients selected with regard to the intended route of administration and standard pharmaceutical practice. The composition may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the composition may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the identity of the individual components, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician and will depend on the particular vascular damaging agent and NO synthase inhibitor in the composition. However the dose of the vascular damaging agent envisaged is, for example, in the range 10-1000mg/m^2 body surface, preferably 20-200mg/ m^2 and that for the nitric oxide inhibitor 1-1000mg/m^2, preferably 5-500mg/ m^2. A unit dose form of the vascular damaging agent as, for example, a sterile solution for injection will usually contain, for example, 40-400mg of the active ingredient. A unit dose form of the nitric oxide synthase inhibitor as, for example, a sterile solution for injection will usually contain, for example, 10-1000mg of the active ingredient. A unit dose form of a composition containing both a vascular damaging agent and a nitric oxide synthase inhibitor as , for example, a sterile solution for injection will usually contain, for example, 40-400mg of the vascular damaging agent and 10-1000mg of the nitric oxide synthase inhibitor.

The composition of the invention may be administered as a sole therapy or in combination with other treatments. For the treatment of solid tumours the composition may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; enzymes, for example aspariginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab; and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

In a further embodiment of the invention we provide the use of a compostion of the invention for the preparation of a medicament for the treatment of a disease involving active angiogenesis.

The invention will now be illustrated by the following Examples in which biological assays are used to illustrate the invention:

Induction of necrosis

Mice bearing either CaNT or SaS tumours were treated with the test compound and tumours excised after 24h, fixed in formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Sections were scored based on area of necrosis as follows:

% necrosis	score	% necrosis	score
0-10	1	51-60	6
11-20	2	61-70	7
21-30	3	71-80	8
31-40	4	81-90	9
41-50	5	91-100	10

Control tumours had mean scores of 2.0 (CaNT) and 1.0 (SaS).

EXAMPLE 1

In this assay the effect of a given dose of either a vascular damaging agent or a nitric oxide synthase inhibitor administered alone can be compared with the effect of a combination of the two agents.

Table 1: Enhancement of Combretastatin A4 phosphate (CA4P) activity in SaS tumours by coadministration of L-N^G-nitroarginine (L-NNA)

Treatment	Necrosis score ±SEM (n)
None	1.0±0 (10)
CA4P, 500mg/kg	1.7±0.7 (3)
L-NNA, 10mg/kg	2.0±1 (3)
CA4P, 500mg/kg + L-NNA 10mg/kg	9.0±0 (3)

EXAMPLE 2

Table 2: Enhancement of Combretastatin A4 phosphate (CA4P) activity in SaS tumours by coadministration of 2-amino-4-methylpyridine (AMP)

Treatment	Necrosis score ±SEM (n)
None	1.0±0 (10)
CA4P, 500mg/kg	1.7±0.7 (3)
AMP, 10mg/kg	1.0 (2)
CA4P, 500mg/kg + AMP 10mg/kg	4.5 (2)

EXAMPLE 3

Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after intra peritoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μm sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels.

Table 3: Enhancement of Combretastatin A4 phosphate (CA4P) activity in CaNT tumours by coadministration of L-N^G-nitroarginine (L-NNA).

Treatment	Vascular Volume % ±SEM (n)
None	2.35
CA4P, 25mg/kg	1.03±0.14 (4)
L-NNA, 10mg/kg	2.45±0.04 (3)
CA4P, 25mg/kg + L-NNA 10mg/kg	0.63±0.25 (3)

CLAIMS:

1. A composition for the treatment of a disease involving active angiogenesis which comprises a vascular damaging agent other than a cytokine releasing anticancer agent together with an inhibitor of the formation or action of nitric oxide in a mammalian system.

2. A composition for the damage of the formation of new vasculature by angiogenesis comprising a combination of a vascular damaging agent other than a cytokine releasing anticancer agent and an amount of an inhibitor of nitric oxide synthase in an amount sufficient to augment the effect of the vascular damaging agent.

3. A composition according to claim 2 wherein said vascular damaging agent is selected from a tubulin-binding agent or an antibody targeted to vasculature.

4. A composition according to claims 2 and 3 wherein the nitric oxide synthase inhibitor is selected from a derivative of arginine, ornithine, lysine, citrulline, S-alkylthioureas or aminoguanidine.

5. A composition according to claim 4 wherein the nitric oxide synthase inhibitor is an N^G-substituted L-arginine selected from N^G-nitro–L-arginine and alkyl esters thereof, N^G-methyl-L-arginine and N^G-amino-L-arginine.

6. A composition according to claim 4 wherein the derivative of ornithine is L-N6-(1-iminoethyl)-ornithine.

7. A composition according to claim 4 wherein the derivative of lysine is L-N6-1-iminoethyl)-lysine.

8. A composition according to claim 4 wherein the derivative of citrulline is selected from L-thiocitrulline, L-homothiocitrulline or an S-alkylthiocitrulline particularly S-methyl-L-thiocitrulline.

9. A composition according to any one of claims 1 to 8 which also comprises a pharmaceutically acceptable excipent appropriate to the method of administration.

10. A composition according to any one of claims 1 to 9 wherein the composition is in the form of a kit, one part of the kit containing the vascular damaging agent and the second part of the kit the nitric oxide inhibitor.

11. Use in the preparation of a medicament for the treatment of disease involving active angiogenesis and containing a vascular damaging agent other than a cytokine releasing anticancer agent characterised in that the medicament also contains an amount of an inhibitor of formation or action of nitric oxide sufficient to augment the effect of the vascular damaging agent.

12. Use according to claim 11 wherein said inhibitor of formation or action of nitric oxide is a nitric oxide synthase.

13. A method of treatment for a mammal having a disease involving active angiogenesis said method comprising administration of a vascular damaging agent other than a cytokine releasing anti cancer agent and an amount of an inhibitor of formation or action of nitric oxide in amount sufficient to augment the effect of the vascular damaging agent.

14. A method according to claim 13 wherein the vascular damaging agent and nitric oxide inhibitor are administered substantially simultaneously but separately to the mammal under treatment.

15. Use of inhibitors of nitric oxide formation or action in the preparation of a medicament for augmentation of the effects of a vascular damaging agent other than a cytokine releasing agent.